MODELING ALZHEIMER'S DISEASE: A STATISTICAL APPROACH TO UNDERSTANDING PATHOGENESIS ACROSS BRAIN REGIONS

An Undergraduate Research Scholars Thesis

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ABSTRACT

Modeling Alzheimer's Disease: A Statistical Approach to Understanding Pathogenesis Across Brain Regions

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With a rapidly aging U.S. population, Alzheimer's disease is a growing public health concern. Key to the success of future Alzheimer's disease psychopharmacological clinical trials is understanding its complex pathogenesis with sophisticated statistical models. Presently, the literature has several models of Alzheimer's disease pathogenesis that utilize fluctuations in biomarkers as the focal point of understanding progression across symptomatic states. Recent research has implicated regional volumetric changes in specific brain regions as one such biomarker of interest. However, the principal models are fundamentally theoretical, and these models are not derived purely from samples of clinical populations within a sophisticated statistical framework. Thus, these theoretical models are yet to be completely validated. Additionally, although some models have analyzed volumetric data from specific brain regions, no such model has assessed volumetric changes cross-regionally to document Alzheimer's disease pathogenesis relative to healthy controls in a large, robust sample.

This model analyzes the relationship among four crucial brain regions impacted by Alzheimer's disease—the hippocampus, entorhinal cortex, fusiform gyrus, and the middle temporal gyrus—using cross-sectional MRI data from a large study of Alzheimer's disease patients and controls.

Results demonstrate a sequence through which we can understand where along the Alzheimer's disease symptom spectrum each brain region becomes pathological relative to healthy controls. Understanding the neurodegenerative sequence of the hippocampus, entorhinal cortex, fusiform gyrus, and middle temporal gyrus is critical to our understanding of Alzheimer's disease pathogenesis. Clinical implications include earlier and more accurate differential diagnosis, elucidation of disease subtypes, and future directions for pharmacological trials.

DEDICATION

First, I would like to dedicate my thesis to my grandmother whose death due to Alzheimer's disease inspired me to get involved in the fight to end Alzheimer's disease. Her spirit of service and humility lives on inside my family and me. Next, I would like to dedicate my work to my parents for both unconditionally supporting me and helping me get to the place I am today. Finally, I would like to dedicate my work to the hardworking staff at Texas A&M LAUNCH, specifically those who work with the Texas A&M Honors program. The mentorship, support, and encouragement from staff members like Austin Ford, Dr. Jonathan Kotinek, Dr. Sumana Datta, Adelia Humme, Wallace Fanning, and many others has inspired me to not only strive for my own success, but stir up a passion for learning among my peers at Texas A&M University as well.

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Data used in the preparation of this thesis were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. For the purpose of this project, the Balsis lab received approval from the Texas A&M University Institutional Review Board, study number: IRB2014-0206D.

CHAPTER I

INTRODUCTION AND BACKGROUND

For a rapidly aging U.S. population, dementia is one of the greatest research and public health priorities. Alzheimer's disease (AD) is the most prevalent form of dementia, affecting millions of relatively older U.S. citizens and tens of millions of people internationally (Alzheimer's, 2015; Plassman et al., 2007; Rafii & Aisen, 2015). Cognitive decline due to AD is devastating and expensive, with an estimated $153 billion spent in 2015 on caring for AD and dementia patients (Alzheimer's, 2015).

As no cure for AD has been discovered, early and precise diagnosis is a key priority of research and clinical efforts. However, AD can only be confirmed with absolute certainty in a post-mortem assessment of brain tissue in autopsy (Khachaturian, 1985, The Alzheimer's Association Autopsy Network, n.d.). Various methods are used in differential diagnosis of AD, including neuropsychological assessments (e.g. the ADAS-cog, the MMSE, etc.) and Magnetic Resonance Imaging (MRI). These diagnostic tools are not perfect and are not universally available in different clinical settings, thus inspiring further research to refine these clinical tools with the aim of achieving an earlier and more precise diagnosis.

Typically, AD usually affects different regions of the brain in a general sequence of neurodegeneration (Ray & Zhang, 2010). Results from previous in vivo and post-mortem neuroimaging research indicate that the disease initiates in the temporal lobe, affecting working memory and language (Fox, Crum, Scahill, Stevens, Janssen, & Rossor, 2001; Hardy, Mann,

Wester, & Winblad, 1986; Masdeau, Zubieta, & Arbizu, 2005). Eventually, it spreads toward the frontal lobe affecting control processes and logical thought. From there, the disease spreads across the parietal lobe and into the occipital lobe affecting basic perceptual processes (Wenk, 2003). It then moves into the cerebellum, affecting balance. In its latest stage, AD reaches the brain stem, resulting in autonomic dysfunction such as difficulty breathing and arrhythmia (Lee, Ryan, Andreescu, Aizenstein, Lim, 2015). Although there is ample evidence of this general progression throughout these major divisions in the brain, less is known about the sequence of neurodegeneration across sub-regions of a single lobe. Specifically, degeneration within the temporal lobe has been the target of much inquiry recently as it is affected very early in the disease process (Masdeau, Zubieta, & Arbizu, 2005).

Within the framework of current AD research effort is biomarker research emphasized on solidifying a verifiable AD pathogenesis model in the temporal lobe. Such a model would allow clinicians to understand the neuroanatomical and physiological processes associated with AD-related cognitive decline. One area of biomarker research aims to assess correlations between volumetric changes in brain regions—specifically, the hippocampus, entorhinal cortex, fusiform gyrus, and middle temporal gyrus—during AD pathogenesis (see Biomarker Models Review). These four regions are presumed to be affected by AD because of the role they play in cognitive processes that deteriorate during AD-related decline (see Neuroanatomical Review).

Neuroanatomical review

Hippocampus

Located in the medial temporal lobe below the cerebral cortex, the hippocampus is the hallmark structure impacted in cognitive decline due to AD. In a review of ADNI papers, Weiner et al. (2012) note that "among the structures of the temporal lobe, hippocampal atrophy is the best studied structural biomarker, as it is one of the earliest structures to degenerate in AD." Hippocampal atrophy due to AD is associated with general delayed memory recall (Convit et al., 1997), as well as declines in episodic (Philippi et al., 2015; Rémy, Vayssière, Saint-Aubert, Barbeau, & Pariente, 2015) and spatial memory (Ezzati, Eslami, Lipton, Katz, Sliwinski, & Lipton, 2015).

Entorhinal cortex

Found in the medial temporal lobe, the entorhinal cortex serves as the primary interface of afferent information to the hippocampus from the neocortex. The entorhinal cortex receives projections from various cortical areas (Vadderah & Gould, 2016). The wide array of afferents that project to the hippocampus via the entorhinal cortex is what provides the repertoire of information that is available in declarative memories (e.g. remembering specific scents in episodic memory).

Fusiform gyrus

Located partially in the occipital and temporal lobes, the fusiform gyrus is separated from the limbic lobe by the collateral sulcus (Vadderah & Gold, 2016). Atrophy of the fusiform gyrus has been implicated in distinguishing the diagnostic categories of mild cognitive impairment (MCI)

from AD (Convit et al., 1997). According to Vadderah & Gould (2016), the fusiform gyrus is implicated in language comprehension, higher order processing of visual information, and complex aspects of learning and memory.

Middle temporal gyrus

The precise function of the middle temporal gyrus is unknown. Research suggests that the middle temporal gyrus may be involved in a variety of higher cognitive processes, such as humor (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996) and semantic processes such as "story-listening," (Lehericy et al., 2000).

Biomarker models review

Current biomarker research aims to model AD pathogenesis with a focus on maximizing clinical utility of AD biomarker assessment (Bateman et al., 2012; Jack et al., 2010; Jack et al., 2013a). Among the research priorities of biomarker assessment is understanding the relationship between volumetric changes in brain regions during AD pathogenesis. Jack et al (2010) presents a "temporal model of AD biomarkers," a model which postulated that *AB* amyloid protein deposition precedes hippocampal atrophy. While hailed as a hallmark of biomarker research, this "amyloid-cascade" hypothesis is constrained and theoretical, synthesizing data from existing biomarker into research into the model. Jack et al. (2013a) proposes a revision of this model that continues to implicate amyloid deposition as the foremost biomarker event in AD pathogenesis.

While still hypothetical, other studies affirm Jack et al. (2013a)'s hypothesis, pointing to *AB* protein deposition as a preclinical biomarker of AD (Benzinger et al., 2013; Villemagne et al.,

2013). Even though Benzinger et al. (2013) supports amyloid deposition as a forerunner of other AD biomarkers (e.g. neurofibrillary tangles), the conclusion that "volumetric and metabolic changes appear at approximately the same time in ADAD mutation carriers" actually challenges Jack et al. (2013a)'s AD biomarker model (Benzinger et al., 2013, E4506).

Amyloid deposition is considered the hallmark of preclinical AD amongst many AD researchers and clinicians, and thus the amyloid-cascade hypothesis has been widely accepted. However, evidence exists that supports both "amyloid-first" and "neurodegeneration-first" biomarker models of AD-related cognitive decline (Jack et al., 2013b). While the amyloid-cascade hypothesis infers a specific sequence of related molecular biomarker events, the causes of a "neurodegeneration-first" sequence are unknown and add to the "controversy of disease pathogenesis," (Jack et al., 2013b).

Understanding the neurodegenerative process of the hippocampus, entorhinal cortex, fusiform gyrus, and middle temporal gyrus is essential to furthering our knowledge of AD pathogenesis. Presently, the majority of the literature proposes models that assess volumetric changes in merely one brain region at a time in an effort to correlate regional brain atrophy with results of clinical neuropsychological assessments (e.g. the MMSE and the ADAS-cog). I am unaware of any model has assessed volumetric changes cross-regionally during Alzheimer's disease pathogenesis relative to healthy controls and intracranial volume. Additionally, the leading models are theoretical versus statistically derived from clinical samples, and therefore have not been validated. This study presents a statistically self-contained model of atrophy in neuroanatomical regions implicated in AD-related decline using a cross-section of MRI data from participants in the Alzheimer's disease Neuroimaging Initiative (ADNI).

CHAPTER II

METHODS

ADNI measurement procedures

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, adni.loni.usc.edu. The ADNI was launched in 2003 as a public-private partnership. The initial goal of ADNI was to recruit 800 participants but ADNI has been followed by two other initiatives, ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of older people who are cognitively healthy, people with early or late MCI, and people with early AD. Demographic information and clinical data used for this study were downloaded from the ADNI data repository (adni.loni.usc.edu) on May 28, 2014. Data for the current analyses come from individuals who completed baseline assessments and had complete data for key cognitive and brain variables described below (n = 1056).

Participants

The analysis for the present study used baseline data from 1056 participants (470 female, 45%) enrolled across all three ADNI phases. Participants were an average of 72.87-years-old (SD = 6.99), highly educated (M = 16.09, SD = 2.77 years), and the majority identified their race as White (n = 970, 92%). Other races represented include Black or African American (n = 52, 5%), Asian (n = 17, 2%), American Indian or Alaskan Native (n = 2, 0%), and Native Hawaiian or Other Pacific Islander (n = 2, 0%); 11 participants (1%) reported that they were more than one race, and 2 participants (0%) were unknown. Thirty-six participants reported their ethnicity as

Hispanic or Latino (3%); 1012 (96%) reported that they were not Hispanic or Latino, and 8 (1%) were unknown.

Baseline diagnoses represented a range of cognitive impairment: 341 (32%) were cognitively normal, 560 (53%) had MCI, and 155 (15%) had presumed Alzheimer's dementia. We included the cognitively normal (CN) participants so that we could model the disease from the continuum of normal aging to pathological aging. In the ADNI, CN participants served as the controls and showed no signs of MCI, or dementia. CN participants had normal cognition (defined as CDR = 0, MMSE between 24-30, and WMS-R Logical Memory II subscale score above education-adjusted cutoffs). MCI participants had a subjective memory concern and significant amnestic dysfunction (defined by CDR = 0.5 plus an abnormal score on the WMS-R Logical Memory II subscale). However, MCI participants had sufficiently preserved functional abilities and global cognition (MMSE score between 24-30), such that they did not meet criteria for AD. Participants were diagnosed with probable dementia of probable AD if they met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et al., 1984). At the time of the ADNI diagnosis, AD participants demonstrated deficits in their global cognition, abnormal memory functioning (based on scores on the WMS-R Logical Memory II subscale), and showed significant concerns with memory (reported by the participant, study partner, or clinician). Finally, participants were excluded if they had a history of significant neurologic disease or brain trauma (including multi-infarct dementia and subdural hematoma).

Measures

We assessed four neuroanatomical regions. In the ADNI sample, participants were evaluated using structural MRI scans to assess cortical volume and neuropsychological tests to assess cognitive performance. The procedures used are readily available online (adni.loni.usc.edu). Here, we describe it briefly:

Neuroanatomical volume

Structural MRI scans enable volumetric measurements of neuroanatomical regions, which can indicate patterns of volumetric changes and brain atrophy associated with AD. We used neuroanatomical volume of four temporal lobe brain regions: entorhinal cortex, hippocampus, fusiform gyrus, and middle temporal gyrus. The MRI procedures in the ADNI protocol were rigorous. Jack et al. (2008) outlines the eleven specific MRI guidelines from the ADNI protocol. Through the consistency mandated by the ADNI protocol, error in the collection MRI data was minimized since the data "must be consistent across sites and over time," (Jack et al., 2008). All values included in the dataset were in cubic millimeters. The range in the dataset for these four variables was determined, and then values were binned into five equal bins (0 through 4). These are the values that were parameterized later in our model.

Cognitive function

Neuropsychological measures of memory, language, visuospatial abilities, and executive function represent the breadth of cognitive decline that occurs in AD and are widely used in clinical research to assess cognitive dysfunction. We analyzed data from measures that capture each of these cognitive domains. To assess memory functioning, we used data from the delayed

recall add on test to the Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, Davis, 1984) and ADAS-Cog word recognition (Rosen et al., 1984), Rey Auditory Verbal Learning Test (Rey, 1964) Learning, Immediate Recall, Delayed Recall, and Recognition indicators. Each measure was binned into up to five equal bins, then those bins were summed across tests, then the sum was binned across five equal bins (0 to 4) to represent our Memory domain. For Language, the same process was carried out for ADAS-Cog Naming (Rosen et al., 1984), Boston Naming Test (Kaplan, Goodglass, & Brand, 1983), and Category Fluency-Animals (adapted from the CERAD Verbal Fluency test; Morris, 1989). For Visuospatial, we used the same procedure for ADAS-Cog Constructional Praxis (Rosen et al., 1984), Clock Drawing Test (Goodglass & Kaplan, 1983) Command and Copy. Finally, for Executive, we used ADAS-Cog Number Cancellation (Rosen et al., 1984), and Trail Making Test A and B (Reitan, 1958; Reitan & Wolfson, 1985). Additional cognitive measures used were the Mini Mental State Examination (Folstein & Folstein, 1975), and the CDR-SOB.

Analyses

The analyses used in this model were aimed at providing a statistical model of the Alzheimer's cascade. This cascade cuts across multiple domains, and thus indicators of the domains have a sigmoid shaped relationship to the continuum of the disease (see Jack et al., 2013). Thus, to model the disease, we need statistical machinery that can identify a core defining dimension of the disease within one domain, then model the ability of the other domains to indicate this domain with sigmoid monotonically increasing function curves. Item response theory (IRT) provides us that machinery. IRT uses multiple markers to statistically define a single latent dimension (in this case, cognitive dysfunction in AD) and simultaneously determine the degree

to which individual markers are related to that dimension with sigmoidal curves (see Jack et al., 2013). For this analysis, we defined the latent continuum in terms of brain volume across four key neuroanatomical regions implicated in AD (entorhinal cortex, hippocampus, fusiform gyrus, and middle temporal gyrus). Then, using IRT software (IRT-LR-DIF), we estimated the item parameters for each brain region. Then we used those items as "anchors" to define our latent continuum, and we determined the extent to which the following MRI biomarkers indicate that latent continuum: entorhinal cortex, hippocampus, fusiform gyrus, and middle temporal gyrus.

CHAPTER III

RESULTS

To assess if our four variables covaried adequately together to fulfill the requirements for an assumption of unidimensionality, an exploratory factor analysis (EFA) in SPSS was conducted to determine if the ratio of first to second eigenvalue was greater than the 3:1 ratio suggested by Embretson and Reise (2000). Results from the EFA indicated the data were indeed sufficiently unidimensional for IRT analyses. Our first eigenvalue was 2.21 and the second was .73, creating a ratio of 3.03. Figure 1 (Appendix A) illustrates the ratios of eigenvalues of the neurocognitive variables assessed in our statistical approach.

Next, a confirmatory factor analysis (CFA) was additionally utilized to determine whether the data were unidimensional enough for IRT analyses. Hu and Bentler (1999) showed that hypothetical structural models are a relatively good fit to observed data when the Tucker-Lewis Index (TLI; Tucker & Lewis, 1973) and comparative fit index (CFI; Bentler, 1990) values are close to .95 and the root mean squared error of approximation (RMSEA; Steiger & Lind, 1980) is less than .06. Using these recommended cutoffs, we concluded that the data (CFI = 0.996, TLI = 0.99, RMSEA = 0.04) were outstanding fits to the specified unidimensional model criteria. A non-significant chi-square test was used to support further this determination. The Chi-Square test 4.94 (2), $p > .05$ was non-significant, providing further confirmation that the data were unidimensional enough for IRT analyses. Taken together, the analyses suggest our data are robustly unidimensional and suitable for the main analyses.

The data were analyzed following the EFA and CFA using the aforementioned IRT software (IRT-LR-DIF). Theta values for each regional brain volume were derived. These theta values were then used to generate four sigmoidal curves, representing the probability of relative volumetric deficits across the four brain regions of interest in this study. Figure 2 elucidates those curves (Appendix A).

Figure 2 is a graphical representation of the probability of volumetric deficits as they vary across brain regions in relation to AD-related cognitive dysfunction. The distribution in curves across the latent continuum (θ) suggests that at lower levels of AD-related cognitive dysfunction, the fusiform gyrus reaches $P = 0.50$ of relative volumetric deficits ($\theta = -3.1$). Accordingly, the entorhinal cortex reaches $P = 0.50$ of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction ($\theta = -1.52$). Further, the hippocampus reaches $P = 0.50$ of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction ($\theta = -0.97$). Lastly, the middle temporal gyrus reaches $P = 0.50$ of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction ($\theta = -0.58$).

CHAPTER IV

DISCUSSION

The model presented in this thesis demonstrates a sequence of neurodegeneration in temporal lobe sub-regions observed in our AD patient cross-section. Our model aligns with previous research, demonstrating that volumetric deficits in the entorhinal cortex are seen at a relatively low level of disease severity. The entorhinal cortex is closely followed by those of the hippocampus and middle temporal gyrus (Du et al., 2004; Killiany et al., 2002). Interestingly, the fusiform gyrus is affected by tissue loss at a much lower level of disease severity than the other neuroanatomical structures in this study. The significant gap between the fusiform gyrus and the remaining three curves suggests that neurodegenration of the fusiform gyrus may possibly be an earlier indicator of pathology. Increased probability in statistically significant volumetric declines in the fusiform gyrus in our model appears at lower levels of cognitive dysfunction. The development of specific neuropsychological assessments geared towards measuring language and object recognition function associated with the action of the fusiform gyrus may be a promising area of research. While it is tempting to associate degeneration in specific brain regions with direct changes in cognition, it is important to recognize, however, that the relationship between the fusiform gyrus and cognitive outcomes, like all other brain regions with their respective functions, are associations and not necessarily casual. Our model suggests that structural changes in the fusiform gyrus may be correlated with subtle cognitive changes that occur earlier in the disease process. As this is a novel statistical model of changes in brain region volumes, further study of the fusiform gyrus is needed to validate this finding.

Limitations of this model must be addressed. First, the present model is cross-sectional versus longitudinal. Longitudinal modeling of disease severity is clinically relevant and of research interest, as Alzheimer's disease is a progressive neurodegenerative disease that follows a general progression. However, cross-sectional modeling is a fruitful base for further research into precise statistical modeling. Second, only one dataset (ADNI) was analyzed in our work. However, this particular dataset is robust and very well characterized, replete with demographic, physiological, and cognitive data points. Additionally, the large sample size (n = 1056) mined from the ADNI database facilitates increases generalizability to clinical populations that are not captured by the database. ADNI is also an ethnically homogenous database; 8% of participants identified as non-white (n = 86). Our analyses should be replicated to cross-validate the model in other more ethnically heterogeneous populations. Thirdly, our model does not consider volumetric changes in other possibly affected regions of the brain. Nevertheless, the four regions presented in this study are of clinical interest, as the literature suggests they relevant to cognitive and functional outcomes, especially in AD patients (O'Brien, 2014; Torisson et al, 2014). Lastly, replication of our model is needed, as this an initial attempt to elucidate the relationship between neuroanatomical volumes and cognitive dysfunction. Nevertheless, this model is mathematically derived and therefore a promising foundation for future replication studies.

Future directions of investigation are numerous. Further research of the function and etiological significance of the fusiform gyrus is clearly necessary; to our knowledge, our model is the first of its kind to implicate the fusiform gyrus as an area of specific interest early on along the continuum of cognitive decline. Our findings suggest that neurodegenration of this brain region may reflect cognitive decline associated with Alzheimer's disease earlier than currently verified

biomarkers. Additionally, studying other structural changes in different regions of the brain may offer insight into specific facets of etiology or pathology. The literature's current understanding of the numerous and complex neuroanatomical structures and pathways in the brain is still considerably limited. There may be additional regions or structures that are relevant to AD pathogenesis and could therefore be added to the present model.

As was mentioned previously, the represented model is cross-sectional in nature. This may be useful for comparisons of group characteristics, but less so at the individual level. Continued utilization of the ADNI and other databases may result in the replication of this model, followed by confirmatory longitudinal models that represent changes in brain region volumes and, accordingly, disease severity over time. Furthermore, both cross-sectional and longitudinal models may be further developed to include a third, highly pertinent dimension that reflects functional status. Such models will be more advanced and represent the multivariate nature of the disease, graphically measuring the correlations between neuroanatomical, cognitive, and functional changes.

Statistical modeling of disease pathology is a powerful research tool that can be applied to various clinical problems. Although not mentioned previously in this thesis, our approach to modeling AD statistically can be extended to create similar statistical models that examine other hallmarks of AD pathology. For example, we are in the process of deriving an empirical model of neuropsychiatric symptoms (e.g., depression, hallucinations, anxiety) along the AD continuum. Neuropsychiatric symptoms due to AD or comorbid pathology (e.g., Schizophrenia) are common in AD patient populations (Lyketsos et al., 2011). It is possible that modeling these

non-cognitive biomarkers may provide a fresh perspective on the disease that would be clinically relevant and have high utility.

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APPENDIX A

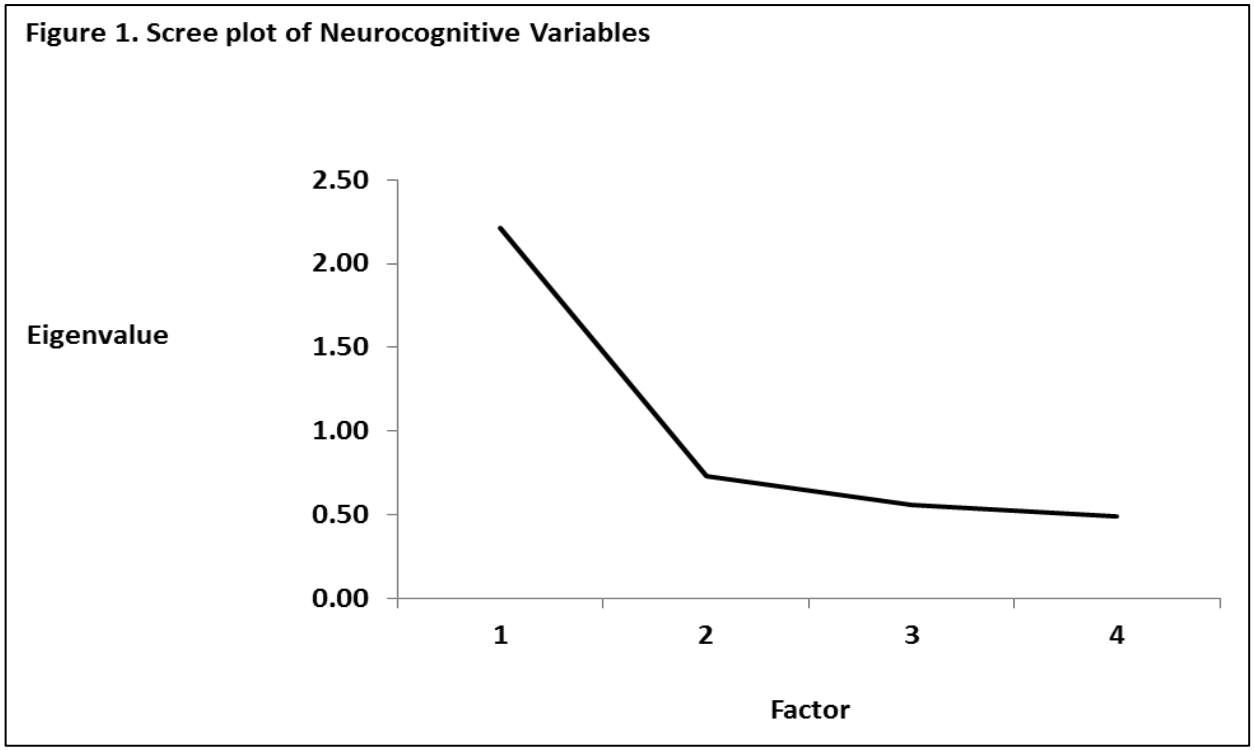

Figure 1. Scree plot of Neurocognitive Variables. This graph illustrates the ratios of eigenvalues of the neurocognitive variables assessed in our statistical approach. This Exploratory Factor Analysis (EFA) was the first step in validating that our AD dysfunction continuum was sufficiently unidimensional for further analyses.

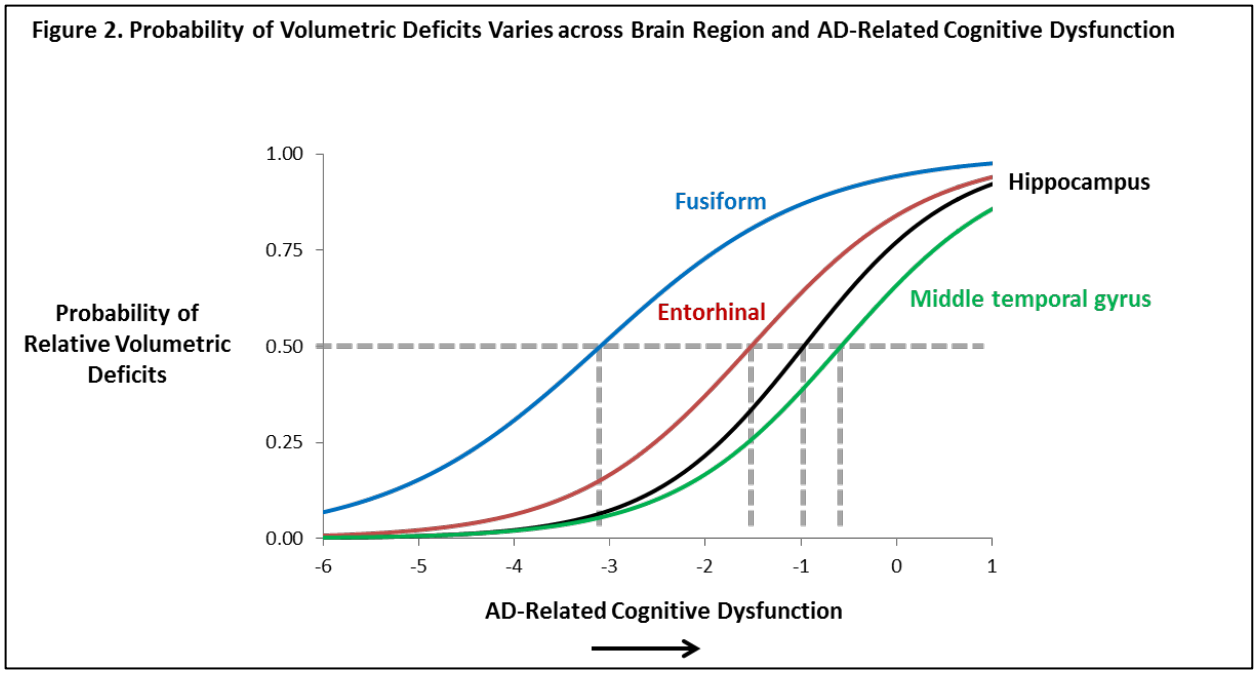

Figure 2. Probability of Volumetric Deficits Varies across Brain Region and AD-Related Cognitive Dysfunction. This figure is a graphical representation of the probability of volumetric deficits as they vary across brain regions in relation to AD-related cognitive dysfunction. The distribution in curves across the latent continuum (θ) suggests that at lower levels of AD-related cognitive dysfunction, the fusiform gyrus reaches P = 0.50 of relative volumetric deficits (θ = -3.1). Accordingly, the entorhinal cortex reaches P = 0.50 of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction (θ = -1.52). Further, the hippocampus reaches P = 0.50 of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction (θ = -0.97). Lastly, the middle temporal gyrus reaches P = 0.50 of relative volumetric deficits at slightly higher levels of AD-related cognitive dysfunction (θ = -0.58).